REMARKS

Claim 39, 41-43, 45, 48, 50, 51, 63, and 68 have been amended herein. Support for the amendments may be found in the specification, for example, in paragraphs 0012, 0024, and 0030. No new matter has been introduced. Claims 75, 122-125, 127-130, 132, and 134 stand withdrawn. Claims 30-34, 37-39, 41-48, 50-56, 63-75, 122-125, 127-130, 132, and 134 are pending. Applicants have carefully considered all of the Examiner's rejections but respectfully submit that the claims are allowable for at least the following reasons.

Withdrawn Claims

Without rebuttal of Applicants traversal in their prior Response dated October 2, 2008, the Examiner has maintained the withdrawal from consideration of Claims 75, 122-125, 127-130, 132 and 134, for allegedly being directed to non-elected subject matter. For this reason Applicants respectfully reiterate their traverse of the withdrawal of Claim 75. Applicants remind the Examiner that in their April 10, 2007 election of species, Applicants elected "rapamycin and analogs and derivatives thereof" and "wet form of age-related macular degeneration." As stated in their election, then pending Claims 30-75 encompassed these species. In the July 6, 2007 Office Action, the Office examined Claim 75, which depends from Claim 68. Thus, the Office has already recognized that Claim 75 is directed to the elected subject matter and Applicants respectfully request that Claim 75 be restored to non-withdrawn status.

Furthermore, Applicants continue to traverse the withdrawal of Claims 122-125, 127-130, 132, and 134. These claims depend from examined Claims 30, 38, 39, 43, 51, 57, or 63 and are directed to and read on the elected species. Accordingly, Applicants respectfully request that Claims 122-125, 127-130, 132, and 134 also be examined.

Applicants also respectfully point out that, as provided by 37 CFR 1.141, upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

Rejections under § 112 – Written Description

The Examiner rejected Claims 39, 41-48, and 50 under 35 U.S.C. § 112, ¶ 1 as failing to comply with the written description requirement. Specifically, the Examiner alleges that the phrase "immunophilin binding active agent" describes a genus that lacks "any per se

structure/function relationship between the disclosed immunophilin binding active agents and any others that might be found using the claimed method." Office Action, page 2. Applicants have amended Claim 39 and 41-43 to remove the phrase "immunophilin binding active agent" and instead recite specific agents. Accordingly, Applicants respectfully submit that Claims 39, 41-48, and 50 satisfy the written description requirement.

Rejections under § 103

The Examiner rejected Claims 30-34, 37-39, 41-48, 50-56, and 63-74 under 35 U.S.C. § 103(a) as being obvious over Mollison (US 6,015,815) in view of Kulkarni (US 5,387,589). The Examiner argues that Mollison teaches the use of polyethylene glycol and ethanol as solvents used in combination with rapamycin analogues and that it would therefore be obvious to use such ingredients for dissolving rapamycin. The Examiner further argues that Kulkarni teaches the use of rapamycin in a pharmaceutical/ophthalmic formulation, which can be administered by intravitreal injection.

Composition Claims

Claim 30 recites a composition comprising rapamycin and polyethylene glycol that is suitable for ophthalmic administration by injection. Similarly, Claim 38 recites a composition of rapamycin dissolved in polyethylene glycol and ethanol that is suitable for ophthalmic administration by injection. Claim 39 recites a composition comprising polyethylene glycol and another agent for ophthalmic administration by injection. Neither Mollison nor Kulkarni teach or suggest a composition comprising polyethylene glycol for ophthalmic administration by injection. The compositions containing polyethylene glycol with rapamycin analogues in Mollison are only for ***non-opthalmic*** use. Specifically, Mollison only teaches to use polyethylene glycol in compositions "for parenteral injection," in "[s]olid dosage forms for oral administration," in "[l]iquid dosage forms for oral administration," and in "[c]ompositions for rectal or vaginal administration." Mollison, column 11, lines 64-65; column 12, line 52; column 13, line 24; and column 14, line 18. In contrast, for "[t]opical administration ... to the ... surfaces of the ... eye," Mollison teaches to use "ophthalmic vehicles" including "an ointment, vegetable oil or an encapsulating material." Mollison, column 13, line 46-47 and column 14, lines 15-17. In summary, Mollison teaches to use polyethylene glycol for many compositions

including those for parenteral, oral, rectal, and vaginal administration but conspicuously ***omits polyethylene glycol for ophthalmic compositions***.

Accordingly, one of skill in the art would not be taught by Mollison to use polyethylene glycol for an ophthalmic composition and therefore would not use polyethylene glycol in a composition suitable for ophthalmic administration by injection such as allegedly suggested by Kulkarni. Simply put, Mollison provides no reason to the skilled artisan to use polyethylene glycol in a composition for ophthalmic administration by injection. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.") In fact, Mollison's omission of polyethylene glycol for ophthalmic compositions suggests using substances other than polyethylene glycol.

Applicants also note that polyethylene glycol was known to be an eye irritant, thereby teaching away from its use in a composition for ophthalmic injection. *See e.g.*, Polyethylene Glycol Material Safety Data Sheet, page 3, Toxicological Information (attached as Exhibit A).

For at least the foregoing reasons, Applicants respectfully submit that it would not be obvious to one of skill in the art to use polyethylene glycol in the compositions suitable for ophthalmic administration by injection as claimed in Claims 30-34, 37-39, 41-48, and 50. Accordingly, Applicants request reconsideration of the rejections of Claims 30-34, 37-39, 41-48, and 50.

Method Claims

Claim 51 recites treating a human having the wet form of age-related macular degeneration using rapamycin dissolved in polyethylene glycol. Similarly, Claim 63 recites inhibiting the transition from the dry form of age-related macular degeneration to the wet form using rapamycin dissolved in polyethylene glycol. In contrast, neither Mollison nor Kulkarni teach or suggest using rapamycin to treat the wet form of age-related macular degeneration or prevent the transition from the dry form to the wet form. Kulkarni is silent with respect to macular degeneration and Mollison teaches away from using rapamycin for this treatment.

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). With respect to

rapamycin and other known compounds, Mollison teaches that "the need remains for macrocyclic immunosuppressants which do not have the serious side effects frequently associated with immunosuppressant therapy due, in part, to the extended half lives of the immunosupressants." Mollison, column 3, lines 17-22. With respect to the novel tetrazole compounds disclosed by Mollison, Mollison indicates that "the compounds of the present invention was [sic] compared to rapamycin." Mollison, column 7, lines 33-34. It was found that the tetrazole compounds "had a surprisingly substantially shorter terminal elimination half-life ($t_{1/2}$) when compared to rapamycin." Column 8, lines 35-36. Mollison concludes that, compared to rapamycin, "only the compounds of the invention provide both sufficient efficacy (Table 1) and a shorter terminal half-life (Table 2)." Column 8, lines 37-38. Thus, Mollison specifically teaches away from using rapamycin in the methods of treatment that it discloses, including treatment of "senile macular degeneration." "A prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness." M.P.E.P. § 2145(X)(D)(1); *see also KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (stating that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious.").

Furthermore, the tetrazole compounds disclosed by Mollison are significantly chemically distinct from rapamycin. Instead of a tetrazole substituent on the cyclohexyl ring of the compounds in Mollison, rapamycin contains a hydroxy substituent. Hydroxy and tetrazole are not mere homologs of one another and one of skill in the art would not expect that replacing a tetrazole with hydroxy would yield a compound having similar biological activity. A *prima facie* case of obviousness based on structural similarity may generally only be made "when chemical compounds have ***very close*** structural similarities." M.P.E.P. § 2144.09(I) (emphasis added). *See Eisai Co. Ltd. v. Dr. Reddy's Labs Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008) (holding that replacing a trifluoroethoxy substituent with a methyoxypropoxy substituent on a compound that was "[o]therwise ... identical" was not obvious). Accordingly, Applicants respectfully submit that a disclosure of the tetrazole compounds of Mollison to treat senile macular degeneration does not render use of rapamycin obvious for the treatment of the same indication.

Finally, neither Mollison nor Kulkarni mention inhibiting the ***transition of the dry form of age-related macular degeneration to the wet form***. Thus, the cited art fails to teach the methods of Claims 63-67 with ***any compound***, let alone rapamycin.

Accordingly, for all of the foregoing reasons, Applicants respectfully submit that it would not be obvious based on the cited art to administer rapamycin to treat the wet form of macular degeneration or inhibit the transition of the dry form to the wet form. As such, it is submitted that Claims 51-56 and 63-67 are not obvious over the cited art.

Claims 51, 63, and 68 also recite ophthalmically administering a composition comprising polyethylene glycol by placement of the composition into the vitreous or by placement of the composition between the conjunctiva and the sclera of an eye of the human. As discussed above with respect to the composition claims, Mollison does not teach to use polyethylene glycol for ophthalmic administration. Mollison's omission of polyethylene glycol for ophthalmic compositions suggests using substances other than polyethylene glycol. Thus, it would not be obvious to one of skill in the art to use rapamycin dissolved in polyethylene glycol for ophthalmic administration by placement of the composition into the vitreous or by placement of the composition between the conjunctiva and the sclera of an eye of the human. For this additional reason, Applicants respectfully submit that Claims 51-56 and 63-67 are not obvious and also submit that Claims 68-74 are not obvious over the cited art.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

By the foregoing amendments and remarks, the Applicants respectfully submit that they have overcome the Examiner's rejections and request a timely issuance of a Notice of Allowance. If there are any remaining issues that can be resolved via telephone conversation, the Examiner is invited to call the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 10, 2009

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